Smoke, Burns, and the Natural History of Inhalation Injury in Fire Victims:

A Correlation of Experimental and Clinical Data

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Mortality and morbidity in fire victims is largely a function of injury due to heat and/or smoke. While degree and area of burn together constitute a reliable numerical measure of cutaneous injury due to heat, as yet no satisfactory measure of inhalation injury has been developed. In this study, with fluid resuscitation and pulmonary infection eliminated as variables, dose-response curves were constructed as a measure of inhalation injury by exposing burned and unburned animals to smoke of constant temperature and toxicity under conditions similar to the fire situation. In these animals, the natural history of inhalation injury: 1) proved to be a relatively simple function of smoke and burn dosage; 2) appeared to simulate and therefore aid interpretation of the inhalation injury syndromes seen in human fire victims; 3) indicated that within limits [COHgb] measured immediately after injury was directly proportional to, and might prove to be a clinically valuable measure of, absorbed dose of smoke. While fluid resuscitation and pulmonary contamination with bacterial pathogens may be eliminated experimentally, such is not the case with the vast majority of fire victims admitted to burn services with associated inhalation injury. Fluid resuscitation and inhalation of a *Pseudomonas aeruginosa* aerosol were therefore included serially in a study of animals with inhalation injury and burns large enough to require fluid resuscitation. In these animals it was demonstrated that: 1) pulmonary edema occurred in association with too little rather than too much fluid therapy; 2) after aerosol inoculation, fatal bacterial pneumonia was difficult to produce when inhalation injury was associated with no or only small burns, but common when associated with a burn large enough to require fluid resuscitation.

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BECAUSE THE EFFECTS of heat have been measurable for so long, our understanding of fire and burns is really quite advanced. The science of thermodynamics has become extremely sophisticated during the 300 years since Galileo first measured temperature; our clinical understanding of burn injury has expanded tremendously since we learned how to measure the per cent of body surface area burned.

In contrast, smoke and injury due to inhalation were not even recognized as major threats to fire victims until the Cocoanut Grove fire in 1942. Since that time, we have learned relatively little about either, in part because adequate measures of smoke and of inhalation injury have yet to be developed, and in part because variables such as fluid resuscitation and pulmonary infection greatly complicate clinical investigation.

In the present study we have tried to elucidate the natural history of inhalation injury in fire victims by correlating it with animal experiments in which both burn and inhalation injury were numerically quantified and both fluid resuscitation and pulmonary infection were controlled or eliminated as variables. Although rarely if at all mentioned in past studies of this subject, this work emphasizes how much worse the prognosis of inhalation injury becomes when the fire victim also receives a major burn.

Materials and Methods

Because they are free of pulmonary infection and readily available, the animals used were 9-week-old, barrier raised, specific-pathogen-free AJ strain male mice weighing 21.6 ± 2.2 gm (mean ± 1 standard deviation). Though not "germ free," contamination by pathogens was avoided before and after burning, smoke exposure, etc. by housing the animals in Trexler-type inflatable vinyl chambers, plenum-ventilated with filter-sterilized air.

Cutaneous Burns and Fluid Resuscitation

With the animals' trunk hair closely clipped, and under methoxyflurane inhalation anesthesia, all burns in this study ≤20% of the body surface area (BSA) were inflicted by removing a 120 gm brass block from 100° water and immediately applying its 3.61 cm² burning surface to the back of each animal for 5 seconds. The resulting burn occupied a mean of approximately 5% BSA.[5] Burns larger than 5% BSA were inflicted by an appropriate number of applications of similar brass blocks to the back, flanks, and/or abdomen. Although animals regained consciousness within minutes, a 2-hour recovery period was allowed before further experimentation. Of untreated animals injured only by receiving 100°, 5-second burns of 5, 10, or 20% of the body surface, 0%, 17%, and 83% respectively were dead within 2 weeks. Because these mortality rates were not improved by parenterally administered resuscitation with 0.9% sterile saline solution equivalent to 10% or 20% of the body weight (BW), fluid resuscitation was not given and was therefore eliminated as a variable when this type of burn was used. "Sham burn" animals underwent a "burning" procedure identical to that described above except that brass blocks were kept in water at room temperature (23°) prior to application. Animals with "no burn" received no anesthesia and no burn prior to smoke exposure.

To simulate in mice a large human burn responsive to fluid resuscitation,[20,29] brass blocks were heated to only 70° before application for 4 seconds to 25% BSA in methoxyflurane anesthetized mice. In this study, all burns of 25% BSA were inflicted in this way and included all areas caudal to the axillae except the tail, lower extremities, and genitalia. With no fluid resuscitation, 44% of such animals died within 24 hours and none died during the 2 weeks thereafter. Mortality rate was reduced to nil in these animals when a volume of 0.9% sterile saline equivalent to 10% or 20% BW was injected early postburn using the combined IP and/or SC route described by Markley.[20] With fluid resuscitation equivalent to 30% BW, mortality rate was 0% at 24 hours, 8% at 1 week, and 33% at 2 weeks postburn (PB).

Smoke Generation and Inhalation Procedures

Because of the fire environment's great complexity,[9,12] we may never know which components of its atmosphere are responsible for inhalation injury in those who breathe it. In such multivariable situations, however, useful information may often be developed from analysis of experimental dose-response curves, even without knowledge or measurement of specific agents. Data from experimental domestic fires suggest that during the 6–12 minutes following ignition, atmospheric temperature and O_2, CO_2, and CO content within the fire environment change relatively little within ranges which are tolerable for brief periods.[6,10,12] After this interval, typically, these environmental variables change precipitously toward levels incompatible with life for more than a few seconds. To approximate the fire situation, therefore, and make smoke dosage proportional only to duration of exposure, for periods of no more than 12 minutes, animals had to be placed in (not separated by heating, cooling, or condensing tubing from) a chamber where smoke was being generated at a temperature and with an O_2, CO_2, and CO content similar to that observed in the early stages of experimental fires. A search of the literature revealed no description of an apparatus capable of generating smoke to these specifications and therefore, a special machine had to be developed (Fig. 1). It consisted of a stainless steel 12-sided cylinder-like container with an exhaust and three viewing ports at its top and 12 animal-insertion locks in its upper third. In its base was mounted a constant velocity turntable exposing the material to be used as fuel for smoke production to a copper bar thermostatically controlled at a given temperature. As cellulose and cellulose-containing materials are the single most common fuel in house fires,[12,17,28] in these studies a single lot of crude cotton (70% cotton and 30% linters) of the type used to fill mattresses and overstuffed chairs was brought into contact with the copper bar and heated to 400 ± 4° at a rate of approximately 1 gm per minute. The turntable progressively exposed only new material to the copper bar and extinguished the smoldering material shortly thereafter. It was this arrangement which provided for continuous generation of smoke of essentially constant content. A 4 liter/minute flow of air was directed past the heating bar and over a single baffle mounted at the base of a vertical flue located in the center of the 12-sided chamber. As smoke moved up the flue, an electrically heated coil mounted in the flue thermostatically maintained the smoke at a desired temperature as measured near the animals' noses. Complete mixing was assured by a nonpropulsive fan mounted in the flue, and just above this, the animals' noses were directed into the flue by holding the animals virtually immobile but able to breathe with ease in well vented

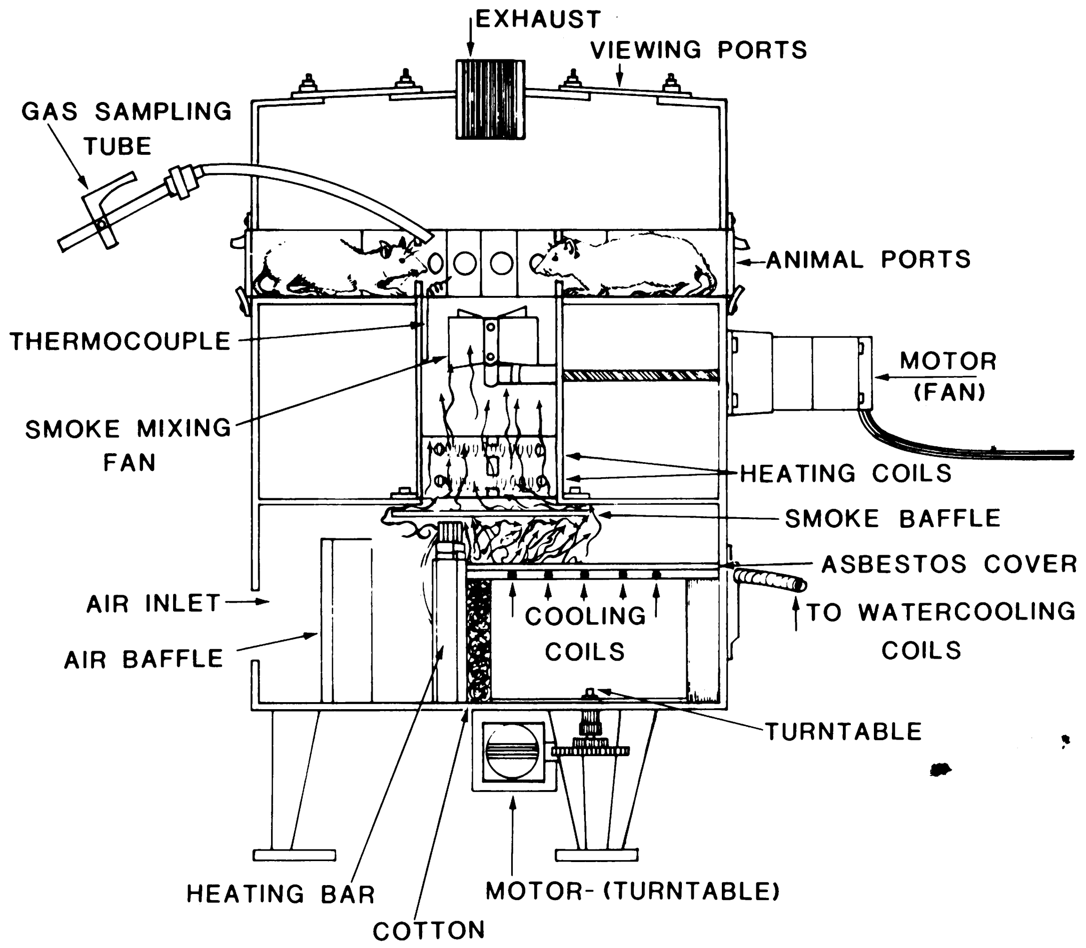

FIG. 1. Cross sectional diagram of inhalation chamber used to generate smoke of effectively constant temperature and toxicity.

plastic chambers inserted through the animal ports. To avoid excessive heating of the turntable during smoke generation, a coil of water-cooled copper tubing was placed over the turntable and separated from smoke by an asbestos insulator. The motors driving the turntable and fan were powered electrically and sterilizable, as were all components of the system.

Aliquots of smoke collected in glass under mercury were taken immediately before and after each exposure of 12 animals or less and measured for O_2 and CO_2 content using a Sholander micro-gas analyzer.[30] Collected at the same time in rubber bags from which CO loss per hour was barely if at all detectable, larger aliquots of smoke were measured for carbon monoxide content using an infrared CO analyzer within two hours of collection. For measurement of CO hemoglobin content [COHgb], heart blood was drawn from groups of three mice within three minutes after smoke exposure and pooled; refrigerated and guarded from exposure to air, the pooled samples were analyzed within two hours for [COHgb] using a spectrophotometer.[18]

With smoke generated as described above, animals were exposed to smoke of $85 \pm 2°$ with an O_2, CO_2, and CO content similar to that observed in the first several minutes of experimental house fires.[6,12] O_2 content of smoke (mean $\pm$ 1 standard deviation) was $19.70 \pm 0.39\%$ measured just prior to exposure and $19.54 \pm 0.47\%$ measured just after. For CO_2 the corresponding values were $0.94 \pm 0.24\%$ and $1.07 \pm 0.23\%$; for CO they were $0.19 \pm 0.03\%$ and $0.19 \pm 0.04\%$.

When appropriate, pulmonary inoculation with a murine derived strain of *Pseudomonas aeruginosa* was carried out one day after exposure to smoke and/or burn by placing the animals in a chamber through which an aerosolized broth culture of bacteria was circulated for one hour.[7] Approximately 2×10^5 organisms could be cultured from each lung of a normal animal sacrificed immediately after inoculation in this way.

Experiments

Relation of Smoke and Burn Dosage to Mortality and Morbidity. Animals were divided at random into four groups: 1) 5% BSA burn-smoke exposure; 2) 10% BSA burn-smoke exposure; 3) no burn-smoke exposure; 4) sham burn-smoke exposure. Because parenteral fluid resuscitation had been shown to be without therapeutic effect in burns of this type, none was given. Within each experimental group, subgroups of no less than 6 animals were exposed to smoke for periods varying from 2 to 12 minutes in duration. Thereafter, mortality rate, activity, and evidence of respiratory distress (labored and/or gasping respirations) were noted at least daily during the subsequent two weeks. Fixed in an expanded condition after transtracheal injection of fixative solution, both lungs were examined histologically in all animals surviving two weeks and in a third of animals surviving to leave the chamber but dying during the two week followup period.

Fluid Resuscitation in Large Burns Associated with Inhalation Injury. Clinically, only fire victims with large burns require fluid resuscitation, and as will be described below, they typically develop "delayed onset" respiratory distress after inhalation of what appears to be relatively low doses of smoke. In this experiment, therefore, pathogen-free animals with 25% BSA burns were exposed to a relatively low smoke dosage of 4 minutes and resuscitated[20] with 0.9% sterile saline using one of three fluid regimens: 1) usual fluid therapy (equivalent to 10% BW); 2) no fluid therapy; or 3) excessive fluid therapy (equivalent to 30% BW). Each group was followed for 2 weeks and the lungs of animals dying during that period were examined histologically.

Exposure to Airborne Bacterial Pathogens After Inhalation Injury. Clinically, whether burned seriously enough to require fluid therapy or not, patients with inhalation injury regularly have their air passages contaminated with nosocomial pathogens, especially if an artificial airway is used. Therefore, the effects of inhaled bacteria on pulmonary histology were demonstrated as follows: Using groups of no less than 12 animals, a 4-minute smoke exposure was given to animals with a small (5% BSA) burn or a large (25% BSA) burn with only the latter receiving resuscitation fluids equivalent to 10% or 30% BW. One day later, these animals together with a group of normal animals were exposed to aerosolized *P. aeruginosa* for 1 hour and both mortality rate and serial pulmonary histology determined thereafter.

Results

Relation of Smoke and Burn Dosage to Mortality and Morbidity. After exposure to smoke for periods of from 2 to 12 minutes, mortality rates in animals with no burn, sham burn, 5% BSA burn, or 10% BSA burn were as shown in Fig. 2. With dose plotted on a logarithmic scale, and response plotted on a probit scale, the data described nearly straight lines. This linear relation of response to duration of smoke exposure established the smoke generated as being of constant toxicity and allowed determination of an approximate LD_{50} for each experimental group.[13]

In general, animals with no burn either died in the

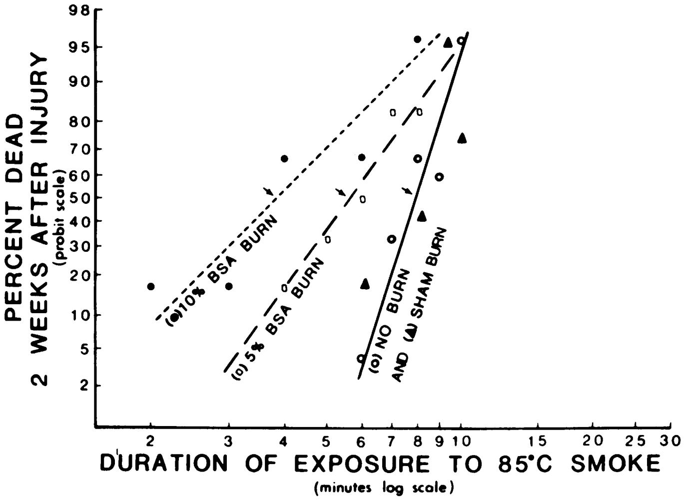

FIG. 2. The relation between dose (duration of exposure to smoke) and response (per cent of smoke-exposed animals dying within 2 weeks) in animals with no or sham burn, and animals with burns of 5% or 10% BSA. Indicated by arrows, the LD_{50} of each group differs significantly ($P < 0.001$) from the others indicated.[4]

smoke chamber or emerged and did well; delayed deaths in animals with no burn occurred only occasionally and with rare exceptions only at their LD_{50} smoke dosage of 8 minutes. In contrast, at smoke dosages of equal or less than 9 minutes, delayed death was the rule in burned animals with 95% of those dying doing so only after they had left the smoke chamber. While sham burned animals had 2-week mortality rates similar to those of animals with no burn (Fig. 2), they occupied a position intermediate between burned animals and those with no burn in that 50% of deaths were delayed after smoke exposure of 9 minutes or less. While there was a striking difference in the frequency of delayed deaths in burned animals (Table 1) as opposed to animals

TABLE 1. *Immediate and Two-week Mortality Rates After Nine Minutes of Smoke Exposure in Mice with No Burn, Sham Burn, or 5%* BSA Burn

Procedure Prior to Smoke Exposure: Cutaneous Burns	Anesthesia: Agent	Anesthesia: Route	Anesthesia: Time before Smoke Exposure	Per Cent Mortality Rate after 9′ Smoke Exposure: Immediate	Per Cent Mortality Rate after 9′ Smoke Exposure: 2 Weeks
None	None	—	—	61	72
Sham	Metaphane	Inhal.	2 hr	29	76*
5% BSA	Metaphane	Inhal.	2 hr	6†	88*
5% BSA	None	—	—	?	?

* Two-week mortality rate differs significantly from immediate mortality rate of the same group ($P < 0.05$).

† Differs significantly from immediate mortality rate of animals with no burn ($P < 0.05$), but not from that in sham burned animals ($0.10 > P > 0.05$).

with no burn, the statistical significance of this remains in doubt because delay also occurred in several sham burned animals. Indeed, there may be no way to establish delayed death as other than an anesthetic effect short of inflicting burns without anesthesia, a procedure not allowed by animal care regulations.[16]

[COHgb] after a given duration of smoke exposure was found to be the same in animals with no burn and those with 5% BSA burn, and to be directly proportional to duration of exposure. After 2 minutes of smoke exposure, [COHgb] was 14–16% in both burned and unburned animals; after 3 minutes of smoke exposure, it was 17–18%; after 7 minutes of smoke exposure, it was 31–32%. After 11 minutes of smoke exposure, [COHgb] was 48% in all animals, a level considered lethal for mice.

In both burned and unburned animals, respiratory distress (RD) upon removal from the smoke chamber was moderate to extreme in severity in all animals after exposure to smoke for 7 minutes or more, but both mild and rapidly diminishing (in minutes to an hour) after smoke exposure of 4–5 minutes or less. Thereafter, at this lower level of smoke exposure the following observations were made.

1. No unburned or sham burned animal died or exhibited further RD.
2. While some animals with 5% BSA burn did die (see Fig. 2), none exhibited further RD and at autopsy no cause of death was found.
3. One or more days postinjury, those animals with burns of 10% BSA that died exhibited a delayed onset pattern of crouched posture and minimal activity associated, in a majority of cases, with gasping and/or labored respiration. When examined at autopsy, however, no cause of death could be found and their lungs appeared normal or exhibited at most a few areas of minor congestion and atelectasis.

Fluid Resuscitation in Large Burns Associated with Inhalation Injury. Among animals receiving 25% BSA burn and 4 minutes of smoke, those receiving fluid resuscitation equivalent to 10% BW had a 25% mortality rate; those receiving resuscitation equivalent to 30% BW had a 42% mortality rate. In both groups, animals dying during the 2-week followup period exhibited variable degrees of RD prior to death, but at postmortem examination none was found to have more than minor pulmonary abnormality even when three times the usual fluid therapy had been given (see Fig. 3a). This was in striking contrast to similarly injured animals receiving no fluid therapy. Of these, 100% died within 2 days, all exhibited severe respiratory distress prior to death, and at postmortem examination their lungs typically showed moderately severe pulmonary edema (see Fig. 3b).

Exposure to Airborne Bacterial Pathogens after Inhalation Injury. After breathing an aerosol of *P. aeruginosa* for 1 hour, all uninjured control animals survived and gave no evidence of RD during a 2-week observation period. Histologically, their lungs showed a brisk polymorphonuclear inflammatory response which peaked at 2 days (see Fig. 4a) and receded rapidly thereafter, but no bacteria were visible. A very similar response was noted in animals receiving a 5% BSA burn and 4 minutes of smoke 1 day prior to inoculation. Their mortality rate of 17% was unchanged by the bacterial challenge. As illustrated in Fig. 4b, pulmonary inflammatory response, if anything, appeared briefer and less intense and no bacteria were visible. Whether given fluid resuscitation equivalent to 10% or 30% BW, however, all animals receiving a 25% BSA burn and 4 minutes of smoke 1 day prior to Pseudomonas inoculation exhibited marked RD prior to death, which in all cases occurred within 3 days. At autopsy (Fig. 4c) the lungs exhibited moderate capillary congestion and moderate parabronchial and paravascular edema with bilateral diffuse, acute, and often severe pneumonitis whether they died spontaneously or were sacrificed at various times PB. Of animals in this group, however, only those dying spontaneously had foci of free bacteria as well as polymorphonuclear leukocytes evident in alveoli throughout each lung suggesting that bacteria became visible because of postmortem proliferation.

Discussion

Because the precise etiology of RD in fire victims is to a large extent unknown and uncertain, classifications similar to that of Stone and based on time of onset are probably the most serviceable and least controversial.[1,31] Table 2 is an attempt to outline the characteristics of RD in fire victims as described in the literature of the past few decades, but reclassified as strictly as possible according to time of onset.

Of the three categories, acute, delayed, and late, late onset syndromes are probably the least specific to fire victims. This is so chiefly because within this group the signs, symptoms, and pathology of RD are either characteristic of recognized phenomena such as aspiration, pulmonary embolus, etc., or are to date indistinguishable from those occurring in many other serious multisystemic diseases. In trying to evaluate the animal model we have described, therefore, we will focus on how well it simulates the acute and delayed onset syndromes seen in man.

Inspection of Table 2 reveals that in addition to the delayed onset of abnormal symptoms, signs and roentgenographic findings, the delayed onset syndrome differs most strikingly from the acute onset syndrome in three details:

1. Patients with RD of acute onset very often have no or only minor burns. In contrast, with rare exceptions patients with the delayed onset syndrome almost always have major burns.[22]

2. While [COHgb] is usually at least moderately elevated in the acute syndrome, [COHgb] is virtually always low or absent when respiratory distress is delayed in onset.

3. Patients with distress of acute onset and with no or minor burn have a mortality rate of approximately 11% or less. This often surprises burn surgeons whose patients with major burns and inhalation injury have quite high mortality rates, especially in those cases where inhalation injury is severe enough to produce acute distress.

With these differences in mind, and with the realization that victims, burned or not, of the severest forms of acute onset distress are frequently found dead "of asphyxia" at the fire scene, acute and delayed onset RD in fire victims may be classified into four distinct syndromes. The distinguishing characteristics of each are detailed in Table 3.

An adequate experimental model should simulate and to some extent elucidate the four distinct syndromes described in Table 3. After analysis, the experimental dose-response curves developed in our laboratory appear to do so. Figure 5 describes the characteristics (i.e., type of RD, presence or absence of burn, [COhemoglobin] and mortality rate) of animals in each of four shaded areas numbered one through four. These characteristics in experimental animals correspond closely to the similarly numbered clinical syndromes described in Table 3. The curve for animals with 5% BSA burns is omitted from Fig. 5 since they did not exhibit the delayed onset RD seen in larger burns at low smoke dosage and therefore resembled unburned animals in that respect. Probably because [COHgb] was measured immediately after smoke exposure experimentally,

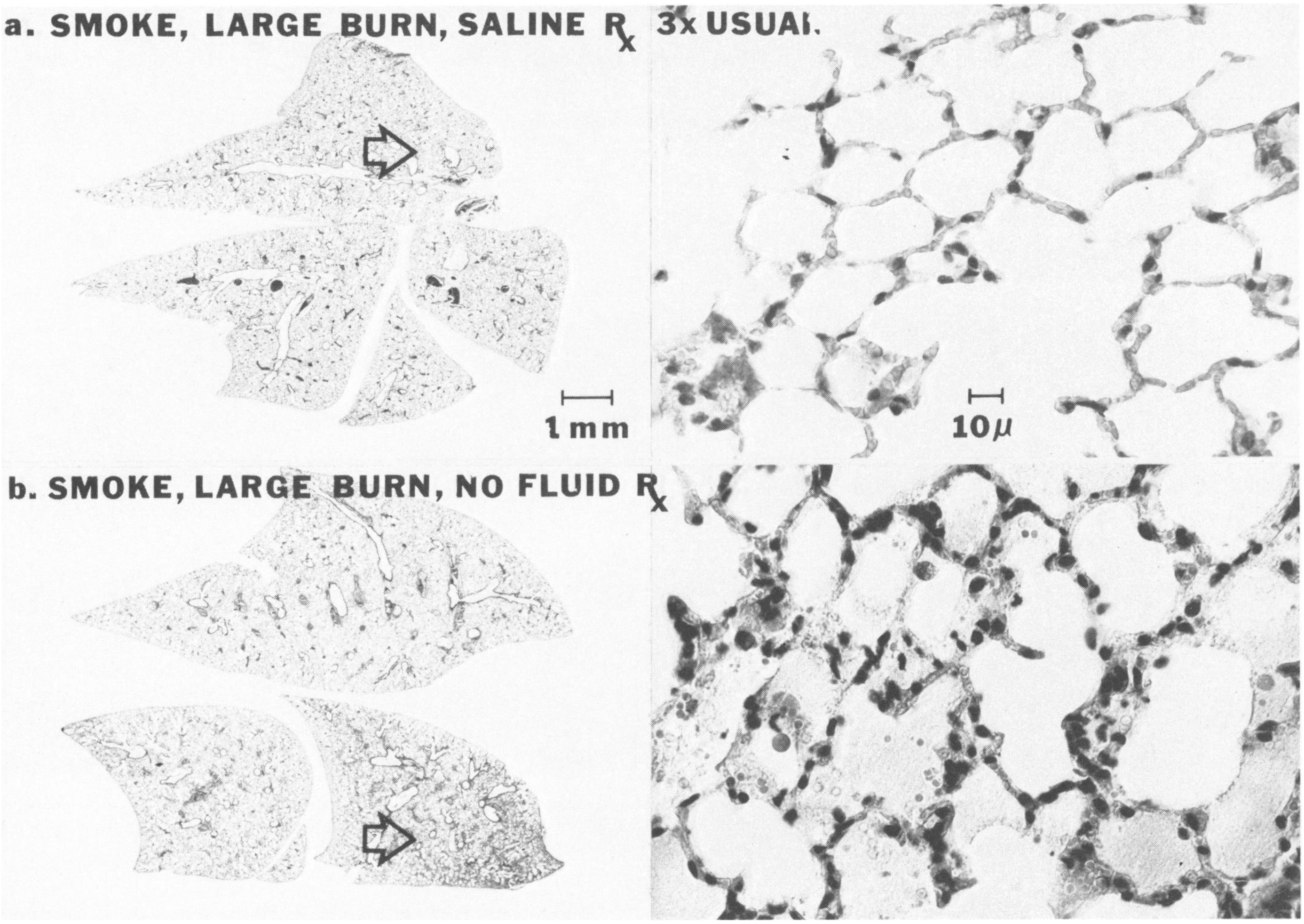

FIG. 3. Effect of fluid resuscitation on postmortem pulmonary histology in pathogen free animals receiving 4 minutes smoke and 25% BSA burn. (a) Minimal histopathology in an animal receiving excessive fluid therapy and dying 3 days PB. (b) Pulmonary edema in an animal receiving no fluid therapy and dying 1 day PB. In each specimen, typical areas are indicated and enlarged at right.

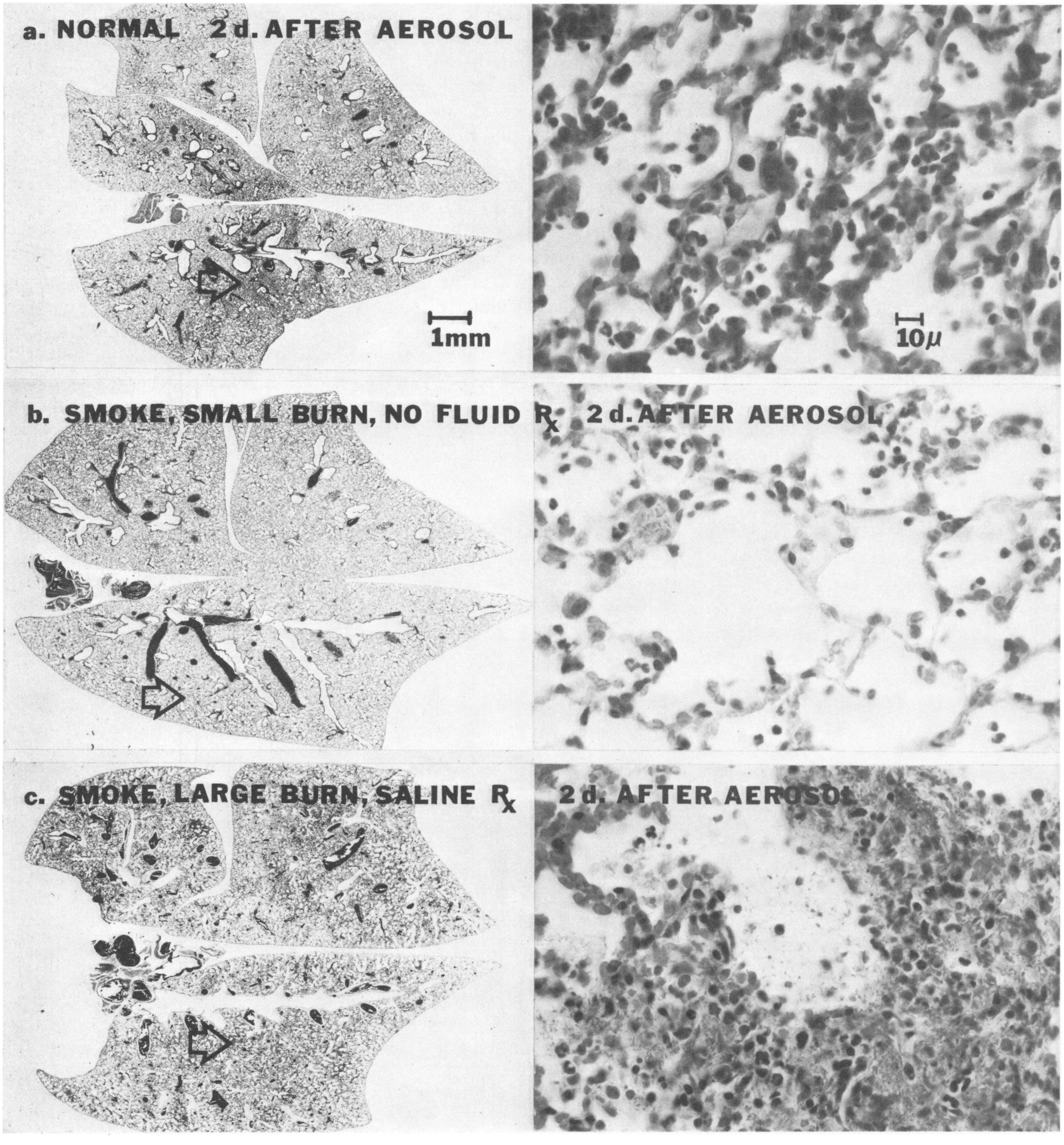

FIG. 4. Effect of airborne pathogens on pulmonary histology. Histologic sections were taken from animals sacrificed (a and b) or dying spontaneously (c) 2 days after aerosol inoculation with *P. aeruginosa*. Burned animals were inoculated 1 day after burn and exposure to smoke for 4 minutes. In each specimen, typical areas are indicated and enlarged at right.

but on admission to the hospital minutes to hours later clinically, at sublethal levels, the [COHgb] measured in each experimental group was slightly higher than usually observed in the corresponding clinical syndrome.

There is some suggestion that even the relatively high frequency of syndromes 1 and 4 and the relative rarity of syndromes 2 and 3 may be explained experimentally (see Table 3 and Fig. 5). Areas 1 and 4 in Fig. 5

lie on the relatively horizontal "tail-end" portions of the S-shaped curves and, therefore, span relatively large portions of smoke-exposure time. Areas 2 and 3 lie on vertical and transitional portions of the curves, spanning relatively brief portions of the possible smoke-exposure time. This, combined with the observation that chances of escape diminish with increasing duration of smoke exposure, may explain the relative frequency of syndrome 1 (burned or unburned victims who never escape) and the relative rarity of syndromes 2 and 3. The relative frequency of syndrome 4 may also be contributed to by the phenomenon of delayed death which is so striking in burned and smoke exposed animals. As indicated in Table 1, however, this must be conjectural pending proof that delayed death can occur independent of anesthetic effects in animals exposed to both burn and smoke.

The parallel between smoke dosage and [COHgb] measured immediately after experimental smoke exposure confirms Zikria's suggestions that [COHgb] determined sequentially after admission and properly extrapolated back to the time of the fire may prove a useful measure of injury due to smoke exposure.[35] Also instructive is the observation that unburned animals exposed to a moderate dose (7 min) of smoke and with a moderate [COHgb] have a strikingly lower mortality rate than burned animals with the same [COHgb] and exposure to smoke (c.f. Table 3 and Fig. 5). This "leap" from one dose-response curve to another may well explain the extreme contrast between unburned or minimally burned patients with acute onset distress and moderate [COHgb] cared for on the pulmonary service with a low mortality rate (syndrome 2), and patients with similar acute distress and [COHgb] but admitted to the burn service with major burns only to exhibit a 60 to 70% mortality rate (syndrome 3).

Based on the above considerations, Table 4 suggests a dose-response relationship between absorbed dosage of smoke and severity of cutaneous burn on the one hand, and mortality rate and respiratory distress on the other.

One obvious difficulty in accepting the experimental model as discussed above is the paucity of findings on histological examination of the lungs. Brief survival

TABLE 2. *Respiratory Distress Syndromes in Fire Victims Listing the Characteristics of Each When Classified by Time of Onset*

Clinical Onset	Acute	Delayed	Late
Days PB	<1	1–5	5 to weeks
Stone's term. e.g.	Acute distress "Overcome" "Smoke poisoning" Heat inhalation	Pulm. edema "Shock lung" "A.R.D.S." "P.-trauma. pul. insuf."	Pneumonia Aspiration Embolus Late overload
Cause	Direct injury lung &/or airway	gases sepsis ← ?BOTH? → in-lung combustion toxins	Complications of burn &/or its Rx
History	Cl. space, smoke; facial or no burns[3,21,27,32]	Better correlation with burn size[1,14]	Varies with etiology
Symptoms & signs	Dyspnea, mania, stupor, wheezes, rales ± stridor[3,21,27,32]	Initially few or none; delayed tachypnea & RD[1,8]	Varies with etiology
X-ray	Sometimes + early (edema, atelec, etc.)[1,3,35]	− Early; later infiltrates s̄ cardiomegaly[8,31]	Varies with etiology
Tests	↑ COHgb often[21,35] ↓ Compliance ↑ Resistance & work[15] + Cytology[2], ^{133}Xe?	Low or no COHgb[1] Compliance ↓ Resistance & work nl. or ↑[24] ? Cytology, ^{133}Xe+[26]	Varies with etiology
Endoscopy	Inflammation[32]	Inflammation +/or soot[25]	Varies with etiology
Pathology	Heat: mostly upper airway damage[23,35] With smoke: bronchiolitis & pul. edema[19,34]	Congestion, edema Pneumonia[8,14]	Varies with etiology
Prognosis	Often fatal at fire scene[34] Relatively good if no major burn[21,33,35] Poor if has major burn[31]	Varies with burn severity[1,8]	Varies with etiology

TABLE 3 *Acute and Delayed Onset Respiratory Distress in Fire Victims Subclassified into Four Clinically Distinct Syndromes*

Syndrome	#1 Acute Onset +/− Burn	#2 Acute Onset 0 or Minor Burn	#3 Acute Onset Major Burn	#4 Delayed Onset Major Burn
Disposition	Dead or moribund at fire scene	To pulmonary service	To burn service	To burn service
Frequency	Common e.g. 71% of victims[11], 64% of early deaths[34]	Relatively uncommon[33,35]	Relatively uncommon e.g. 16% of pulmonary complications[31]	Common e.g. 64% of pulmonary complications[1]
[COHgb]	Often high, e.g. > 50% in 24%, 11 to 49% in 35%[34]	Moderate e.g. > 15% in 84%[35]	Moderate e.g. 17–40%*	Low or absent[1]
Death Rate	100% usually of asphyxia e.g., 64% of deaths < 12 hr. of asphyxia[34]	Low e.g. 0–11%[21,33,35]	High e.g. 65–70%[1,31]	Proportional to BSA burned[1,8]

* LAC-USC experience 1974–75.

might explain the lack of well developed histological findings in untreated victims of high smoke dosage. Quite regularly, however, several days passed before death occurred in burned animals receiving a 4-minute dose of smoke and, as seen in Fig. 5 and Table 4, this was the experimental smoke dosage which seemed to correlate best with inhalation injury as it is commonly seen on a burn ward. Surely if our model were adequate, major histological changes should be seen in these animals; none was, however. The cause of the delayed onset gasping, labored breathing, etc., while due to inhalation injury (none occurred in burned animals not exposed to smoke), was not obviously pulmonary. Could the RD have been toxic or neurogenic in origin? Certainly it was not secondary to fluid resuscitation or pulmonary bacterial infection because for experimental clarity these had been eliminated as variables.

These difficulties led to experiments in which the

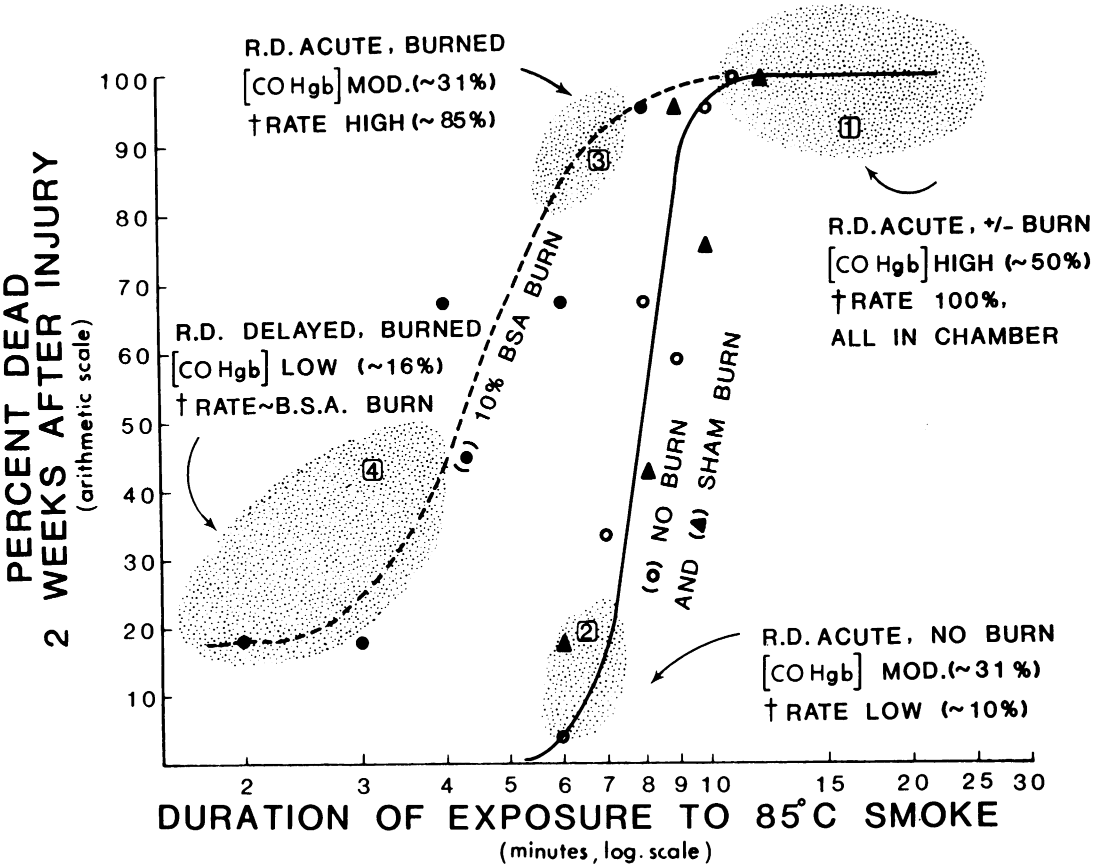

FIG. 5. Dose (smoke exposure) versus response (mortality rate) for mice with no or sham burn and mice with 10% BSA burn with mortality plotted on an arithmetic scale to yield S-shaped curves. Indicated by shaded areas, four groups of animals are described with characteristics corresponding to similarly numbered clinical syndromes of acute and delayed onset respiratory distress (cf. Table 3).

variables of fluid resuscitation and pulmonary bacterial contamination were serially added to the model of inhalation injury as it is most commonly seen on a burn ward, i.e., to animals receiving a major burn and low doses of smoke.

As illustrated in Fig. 3 and with infection still eliminated as a variable, in animals with a large burn and receiving 4 minutes of smoke, RD, wet and edematous lungs, and high mortality rate were found in animals receiving too little rather than the usual 10% BW or 3 times that volume of fluid. Although therapy with fluids with varying colloid and sodium content have yet to be studied in this model, these data suggest that we may have more to fear from insufficient than excessive fluid therapy in seeking to avoid the familiar clinical syndrome of wet, stiff lungs.

As illustrated in Fig. 4, after exposure to the Pseudomonas aerosol, animals with small burns and low dose smoke inhalation did far better at avoiding death and pneumonia than animals with similar inhalation accompanied by a burn large enough to require fluid resuscitation. As the rate of airway cross infection by bacterial pathogens such as Pseudomonas approaches 100% both in pulmonary intensive care units and in burn intensive care units when artificial airways are used, the experimental design employed was not inappropriate although clinically the number of bacteria inhaled is difficult to estimate. The data obtained in the murine model corresponded well with the relatively benign history of inhalation injury as seen on a pulmonary service (that is, accompanied by little or no burn) in contrast to that seen in patients with a major burn.

As illustrated in Figs. 3 and 4, when burns large enough to require fluid resuscitation are used, and contamination by bacterial pathogens is added to the murine model, not only its natural history but its histopathology comes to simulate that seen clinically. These findings lead to important questions about the cause of RD in burn victims with smoke inhalation. Is it a large burn, fluid therapy, or both which after pulmonary bacterial contamination produce the characteristic histology of pneumonia both in our model and in man? Is steroid therapy of inhalation injury perhaps appropriate when accompanied by a little or no burn, but inappropriate when pulmonary susceptibility to infection is increased by association with a large burn? Does delayed onset RD in large burns occur only in the presence of inhalation injury as suggested by Moylan's data,[25] or does it regularly occur when there is no evidence of inhalation injury as in other forms of major trauma? Despite elimination of the need for fluid resuscitation, RD and death were observed in our pathogen-free murine model in patterns strikingly similar to that seen clinically; if the ill effects of pulmonary contamination and imperfect fluid resuscitation could be avoided clinically, would RD and death still occur? Do many of our patients die only with rather than of pneumonia? Hopefully, further efforts to understand the pathophysiology of inhalation injury in fire victims will yield answers to these questions.

TABLE 4. *Apparent Dose Relationship Between Respiratory Distress and Combined Injury Due to Smoke and Cutaneous Burn*

"Dose" or Magnitude of Injury Due to		"Response" Respiratory Distress	
Smoke (dosage)	Cutaneous Burn (severity)	Onset	Mortality Rate
High	Major	Acute	Immediately fatal
High	Minor or 0	Acute	Immediately fatal
Moderate	Major	Acute	High
Moderate	Minor or 0	Acute	Low
Low	Major	Delayed	~ to BSA burned
Low	Minor or 0	Acute Mild, transient	Negligible to 0

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